Final Report

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Stanford University

"Theoretical and Experimental Analysis of the Neural Bases for Learning and Memory"

Principal Investigator: *Richard F. Thompson*

Co-Principal Investigator: Herbert Solomon

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NEUROBIOLOGICAL NETWORK ANALYSIS (Thompson Laboratory)

Our ONR supported empirical work during the past five years has focused on identification of the essential, i.e., the necessary and sufficient, neural memory trace circuitry and the essential memory traces for associative learning and memory of discrete behavioral responses learned to deal with aversive events, using eyelid conditioning (in the rabbit) as the primary animal model but other discrete responses as well. In-so-far as localization of the memory trace itself is concerned, we developed several lines of evidence arguing strongly that it is not in the motor nuclei that generate the behavioral response or in the UR reflex pathways, most notably that lesions and pharmacological manipulations can selectively abolish the CR with no effect on the UR. (see below and Mauk et al., 1982; McCormick et al., 1982a; Thompson et al., 1983). Utilizing an auditory signal detection paradigm we developed strong evidence that with an auditory CS the memory trace is not stored in the CS pathway, at the least the main-line primary auditory relay nuclei. (Kettner et al., 1980; Kettner & Thompson, 1982, 1985).

Our evidence to date demonstrates that the cerebellum is necessary for the learning and memory of eyelid closure and other discrete behavioral responses (see below). When we began this work about eighteen years ago, we had no idea that we would be led to the cerebellum as the key structure that appears to store the essential memory trace. With the advantage of hindsight, it is perhaps not so surprising. The conditioned eyelid closure response is a very precisely timed movement--over the entire effective CS-US onset interval where learning occurs, from about 100 msec to over 1 sec., the learned response develops such that the eyelid closure is maximal at the time of onset of the US. In this sense it is a maximally adaptive response. It is also a very precisely timed "skilled" movement, perhaps the most elementary form of learned skilled movement. Our results strongly support the general spirit of earlier computatinal theories of the role of the cerebellum in motor learning. (Albus, 1971; Eccles, 1977; Ito, 1984; Marr, 1969).

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CEREBELLUM

In the course of mapping the brain stem and cerebellum we discovered localized regions of cerebellar cortex and a region in the lateral interpositus nucleus where neuronal activity exhibited requisite memory trace properties--patterned changes in neuronal discharge frequency that preceded the behavioral learned response by as much as 60 msec (minimum behavioral CR onset latency approx. 100 msec), predicted the form of the learned behavioral response (but not the reflex response) and grew over the course of training, i.e., predicted the development of behavioral learning (McCormick et al. 1981, 1982a, McCormick and Thompson, 1984a and b, Thompson, 1986) (Figure 1).

We undertook a series of lesion studies -- large lesions of lateral cerebellar cortex and nuclei, electrolytic and kainic acid lesions of the interpositus and lesions of the superior cerebellar peduncle ipsilateral to the learned response all abolished the learned response completely and permanently, had no effect on the reflex UR and did not prevent or impair learning on the contralateral side of the body (Clark et al., 1984; Lavond et al., 1985; McCormick et al., 1981, 1982a,b; Thompson et al., 1984). After our initial papers were published, Yeo, Glickstein and associates replicated our basic lesion result for the interpositus nucleus, using light as well as tone CSs and a periorbital shock US (we had used corneal airpuff US), thus extending the generality of the result (Yeo et al., 1985).

CR PATHWAY

The essential efferent CR pathway appears to consist of fibers exiting from the interpositus nucleus ipsilateral to the trained side of the body in the superior cerebellar peduncle, crossing to relay in the contralateral magnocellular division of the red nucleus and crossing back to descend in the rubral pathway to act ultimately on motor neurons (Chapman et al., 1985; Haley et al., 1983; Lavond et al., 1981; Madden et al., 1983; McCormick et al., 1982b; Rosenfield et al., 1985) (see Figure 2).

CS PATHWAY

Lesion and microstimulation data suggest that the essential conditioned stimulus (CS) pathway includes mossy fiber projections to the cerebellum via the pontine nuclei (see Figure 2). Thus, sufficiently large lesions of the middle cerebellar peduncle prevent acquisition and immediately abolish retention of the eyelid CR to all modalities of CS (Solomon et al, 1986) whereas lesions in the pontine nuclear region can selectively abolish the eyelid CR to an acoustic CS (Steinmetz et al, 1987). Consistent with this result is current anatomical evidence from our laboratory for a direct contralateral projection from the ventral cochlear nucleus to this same region of the pons (Thompson, Lavond, and Thompson, 1986) and electrophysiological evidence of a "primary-like" auditory relay nucleus in this pontine region (Logan, Steinmetz, and Thompson, 1986). Electrical microstimulation of the mossy fiber system serves as a very effective CS, producing rapid learning, on average more rapid than with peripheral CSs, when paired with, e.g., a corneal airpuff US (Steinmetz et al., 1986). Electrical microstimulation of appropriate regions of the pontine nuclei - mossy fibers as the CS has the further advantage that a very localized region of cerebellar cortex is necessary for learning and memory of the CR, i.e., localized lesions of cerebellar cortex alone permanently abolish the CR (Knowlton et al., 1986). This, together with our Purkinje cell recording data and US pathway analysis (see below) develops a strong case that memory traces are formed in cerebellar cortex, a structure that seems to have been "designed" for neurobiological and computational analysis.

PURKINJE CELLS - SIMPLE SPIKES

Recordings from cerebellar Purkinje cells in the eyelid conditioning paradigm are consistent with the formation of memory traces in cerebellar cortex. Prior to training, a tone CS causes a variable evoked increase in frequency of discharge of simple spikes in many Purkinje cells in HVI, Crus I and Crus II (Donegan et al., 1985; Foy and Thompson, 1986). Following training, the majority of Purkinje cells that develop a change in frequency of simple spike discharge that correlates with the behavioral response, as opposed to being stimulus evoked, show decreases in frequency of discharge of simple spikes that precede and "predict" the form of the behavioral learned response.

THE US PATHWAY

Small electrolytic lesions in the rostromedial (face) region of the Dorsal Accessory Olive (DAO) portion of the inferior olive have a most interesting effect on the learned eyelid closure response: following the lesion (contralateral to the trained eye) the animals show normal behavioral CRs. But with continued paired training (i.e., tone CS, corneal airpuff US) the unconditioned response extinguished in a manner very similar to

control animals (with electrodes implanted in the DAO but not lesioned) where the corneal airpuff was discontinued and the animals given conventional CS alone extinction training (McCormick, et al., 1985). The effective DAO lesion has no effect on the unconditioned response (UR) to corneal airpuff stimulation.

To our knowledge this is the first report of a central brain lesion that produces extinction of the learned behavioral response with continued paired CS-US training in classical conditioning. This result demonstrates that the essential memory trace is not in the inferior olive -- the animals performed the normal CR following lesions. The result is also supportive of our hypothesis that the DAO-climbing fiber system is a part of the essential US reinforcing pathway.

Perhaps the most extraordinary result we have obtained to date involves microstimulation of the DAO (Mauk et al., 1986). Such stimulation can elicit a wide range of behavioral responses, e.g., eyelid closure, limb flexion or extension, head turn, etc.. the exact location of the stimulating microelectrode determining the nature of the behavioral response, consistent with the organization of somatic sensory projections to the DAO (e.g., Gellman et al., 1983). If this movement-evoking DAO stimulus is now used as a US and paired with a tone CS, the animal learns to perform exactly the same behavioral response (phasic movement) as a conditioned response to the tone CS. Excluding nociceptive components of the somatosensory system, we know of no other system in the brain that can produce this effect. Interestingly, electrical microstimulation of the DAO that serves as an entirely adequate US is not at all aversive to the animal.

Two lines of evidence from electrophysiological recording studies support the notion that the climbing fiber system is the essential US reinforcing pathway. The first involves recording the activity of single Purkinje neurons. As noted above, there are clear and marked changes in the patterns of simple spike discharges of Purkinje neurons (mossy fiber-granule cell-parallel fiber system). But there are also clear and dramatic changes in the patterns of complex spike discharges (climbing fibers from the IO). Prior to training, the onset of the US (corneal airpuff) consistently evokes complex spikes in those Purkinje cells receiving climbing fiber projections from the region of the IO that is activated by stimulation of the eye region of the face. In well-trained animals, the US onset typically does not evoke complex spikes in the appropriate Purkinje cells (Foy and Thompson, 1986). It appears that as the CR develops, climbing fiber activation of the Purkinje cells by the US becomes markedly attenuated.

In current preliminary studies we have obtained more direct evidence by recording activity of neurons in the dorsal accessory olive activated by the corneal airpuff US onset (Steinmetz, Donegan and Thompson, in preparation). US alone presentations consistently evoke a phasic increase in responses of these neurons (US onset evoked). As the behavioral CR (eyelid response) begins to develop, this US onset evoked response in dorsal accessory olive neurons becomes markedly attenuated. Indeed, in a well-trained animal, US onset evoked activity may be completely absent in the dorsal accessory olive on trials where the animal gives a CR. But US <u>alone</u> presentations still evoke the same onset response that the US evoked prior to training.

Collectively, the evidence reviewed above demonstrates that the cerebellum is essential for the category of "procedural" memory we have studied. It also builds an increasingly strong case that the essential memory traces are stored in very localized regions of the cerebellum. Our current working hypothesis is that memory traces are formed in regions of cerebellar cortex where CS activated mossy fiber - granule cell - parallel fiber projections and US activated climbing fiber projections converge. Similarly, we hypothesize that traces are formed at regions of convergence of mossy fibers and parallel fibers in the interpositus nucleus.

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* = Publications supported by the contract.

Stochastic Models and Data Analysis

Working jointly with the Thompson Laboratory, a group of statisticians under Professor Solomon looked into neuron models and data analysis in connection with experimentation performed by the Thompson group. In addition to individual interaction, a number of seminars on neural science models occurred. The following gives some indication of the seminars conducted and the diversity of the participants.

Synaptic Interaction Models
Prof. David Brillinger, Statistics Dept., UC Berkeley

Learning-Logic
David Parker, Stanford Linear Accelerator Center, Stanford University

Neurocognitive Pattern Analysis From Scalp Recordings
Dr. Alan Gevins, E.E.G. Systems Laboratory, San Francisco

An Introduction To Current Research In Cellular Automata
Prof. Persi Diaconis, Statistics Dept., Stanford University

The Physiological Basis Of Mental Images
Prof. Walter J. Freeman, U. of California

Nearest Neighbor Rule Classification Of Time Series: Applications To Exploratory EEG Population Screening Problems
Prof. Will Gersch, Dept. of Information and Computer Sciences, U. of Hawaii

Brain Substrates Of Simple Learned Responses
Prof. Richard Thompson, Psychology Dept., Stanford University

Several investigations led to the development of technical memoranda. Listed below, by author and title, are some of the memoranda.

Doss, Hani and Marhoul, Joseph. "Some Graphical Methods For Assessing The Dependence Structure Between Neuronal Spike Trains"

Doss, Hani. "On Estimating The Dependence Between Two Point Processes"

Doss, Hani. "On Estimating The Cross-Correlation Between Neuronal Spike Trains"

Iyengar, Satish. "Stochastic Models And Statistical Methods For Multivariate Point Processes"

Iyengar, Satish. "Hitting Lines With Two-Dimensional Brownian Motion"

Iyengar, Satish. "Data Analysis And Stochastic Modeling For Networks Of Neurons"

Huffer, Fred. "Inequalities For The M/G/∞ Queue And Related Shot Noise Processes"

Gersch, Will. "Nearest Neighbor Rule Classification Of Time Series In Exploratory Population Screening Problems"

Gersch, Will. "Modeling Multivariate Covariance Nonstationary Time Series And Their Dependence Structure: An Application To Human Epileptic Event EEG Analysis"

Gersch, Will and Kitagawa, Genshiro. "Smoothness Priors In Time Series"

Gersch, Will and Kitagawa, Genshiro. "Smoothness Priors Transfer Function Estimation"

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